Practical Approach to Andropause (PADAM) and Androgen Therapy

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1. INTRODUCTION

- 남성은 여성과 달리 수태력이나 생식선기능의 갑작스런 감퇴를 경험하지 않으나 남성의 노화는 고환 및 부신으로부터 생산되는 testosterone의 점진적인 감소를 동반한다.
  그러므로 폐경기 여성을 연상케하는 "Andropause" 또는 "Male Climacteruim" 보다 **"Partial Androgen Deficiency of the Aging Male (PADAM)"** 가 적절한 용어로 인정되고 있다.
- 노인남성
  내분비변화가 뇌, 골대사, 근육질과 신체지방분포, 성기능, 적혈구 생산, 심혈관계에 영향을 미칠 수 있는 것으로 증명.
  ==> 폐경기 여성에 대한 여성호르몬 보충요법 처럼 이러한 변화를 부족한 남성호르몬을 보충함으로써 예방 내지 치료하여 노인 남성의 삶의 질을 향상시킬 수 있지 않을까 하는 연구가 최근 활발히 전개되고 있다.
  그러나 노인 중 어떤 남성을 남성호르몬 보충요법의 대상으로 할 것인지에 대해서는 아직 명확한 기준이 없다.
- women: complete and abrupt cessation of ovarian function during the menopause.
  aging men: largely maintain their testicular androgen production.
  --> partial decrease in testosterone levels with aging
- mechanism for an age-associated decline in testosterone production
  1) defects in the hypothalamic-pituitary-testicular axis
  2) an increase in sex hormone binding globulin levels
  3) environmental factors
  4) medication use
  5) chronic illness

2. EPIDEMIOLOGICAL CONSIDERATIONS

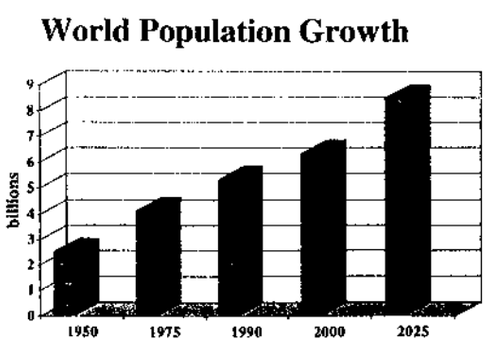


Figure 1. United Nations projections for world population growth in a lifetime (years 1950 to

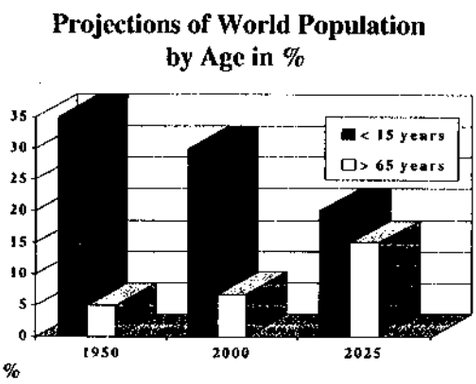


Figure 2.. Changes in the "non-productive" world population between 1950 and 2025. The steady decrease in the under 15 year-olds is matched by an increase in those over 65 years of age. These projection together with the ones in Figure 1. Point to a rapidly growing old world population.

--> there will be a fast increase in the number of elderly (>65yrs) and in the old (>85). Over that period the number of elderly persons will triple, while the number of children will diminish from 35 to 20%.
The Earth, therefore, in hosting a rapidly aging humanity.

3. MALE REPRODUCTIVE PHYSIOLOGY

1) Introduction

Testis: two functions

- spermatogenesis : seminiferous tubules
- secretion of steroid hormones(androgens) : Leydig cells

==> " hypothalamic-pituitary-gonadal axis" 에 의해 조절
anterior pituitary controls these functions through the secretion of the gonadotropins (LH, FSH)

==> In turn, the anterior pituitary: regulated by the hypothalamic secretion of GnRH

2) The Hypothalamus

- pulse generator for the cyclical secretion of pituitary and gonadal hormones.
- hypothalmic releasing H --> portal vascualr system
  --> ant. pituitary gland.
- GnRH
  * released to the portal circulation in pulses occurring in the average of 1 pulse every 70-90 minutes.
  * very short half-life (2-5 minutes)
  * pulsatile secretion of GnRH appears to be essential for the stimulatory effects on LH and FSH release
  * variety of influences including age, diet, stress, and exercise may effect the level of GnRH secretion

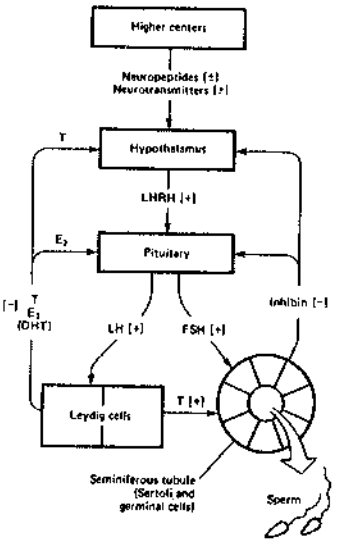


Figure 45-1. Hypothalamic-pituitary-gonadal axis. DHT = dihydrotestosterone; E_2 = estradiol; FSH = follicle-stimulating hormone; LH = lutelnizing hormone; LHRH = lutelnizing hormone releasing hormone; T = testosterone; + = positive influence; - = negative influence. (Reproduced, with permission, from McClure RD: Endocrine investigation and therapy. Urol Clin North Am 1987;

3) Anterior Pituitary

- GnRH influences the release of the two primary pituitary hormones (LH and FSH)
  ---> regulate testicular function
- Pituitary H. : both glycoproteins composed of two polypeptide chain subunits
  - alpha-units --> similar to other pituitary hormones (TSH, hCG)
  - beta-units --> biological and immunological activity
- longer half life of FSH in circulation is reflected by a more constant serum level than that of the more rapidly metabolized LH
  LH: single measurement of of circulating LH may be as much as 50% above or below mean integrated hormone concentrations.
- FSH, LH: increased with age, while prolactin declined.
- serum levels of the estrogens, estrone and estradiol : age invariant or increase slightly

4) Testis

(1) LH : high-affinity cell-surface receptors on the plasma membrane of Leydig cells.

--> stimulates a membrane-bound adenylate cyclase to enhance the formation of cAMP

activation of the catalytic subunit of the enzyme.

activated Leydig cell protein kinase operates through several steps to stimulate

the synthesis of enzymes of testosterone synthesis

(2) FSH

epithelium of the seminiferous tubule: primary site of action of FSH.

--> cell surface receptor에 부착

--> cAMP-dependent protein kinase

--> stimulates RNA

--> protein synthesis

synthesis of androgen-binding protein

aromatase enz.(T-> estradiol)

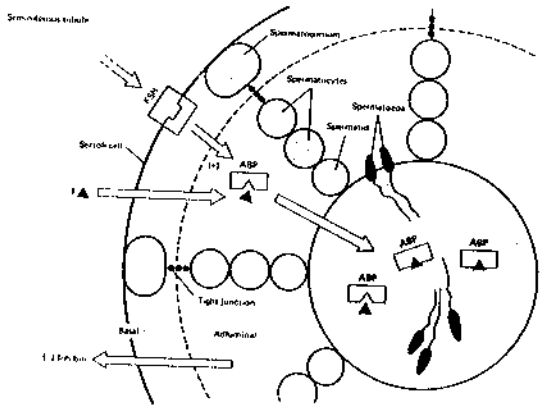


Figure 45–4. Schematic representation of the seminiferous tubule. Follicle-stimulating hormone (FSH) and testosterone (T) act on the Sertoli cells, which produce both androgen-binding protein (ABP) and inhibin. (Reproduced, with permission, from McClure RD: Endocrine investigation and therapy. *Urol Clin North Am* 1987;14:471.)

5) Feedback control of gonadotropins

- LH secretion

exogenous GnRH

--> magnitude of the LH rise

estradiol 투여시 LH 분비 감소

T 투여시 LH 분비 정상

의미) estradio acts at the pituitary level

T acts at the hypothalamic level

cf) Estradiol)

produced ┌ the testes

└ peripheral conversion of androgenic precursors.

--> Although the blood level is low compared to that of T, it is a more potent inhibitor of LH and FSH secretion.

- FSH secretion

F-B control of FSH secretion: more controvereial than that of LH

inhibin : important in the feedback regulation of FSH

produced by the Sertoli cells of the testes.

two subunits

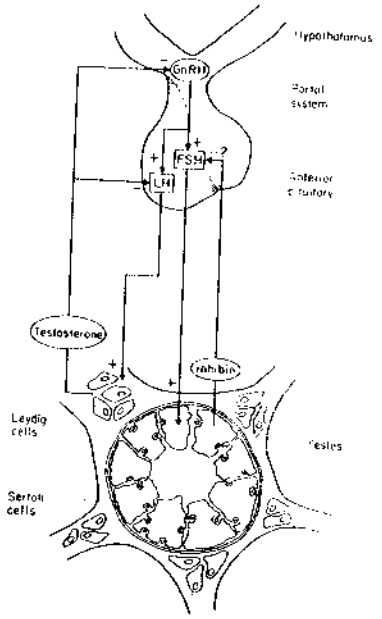


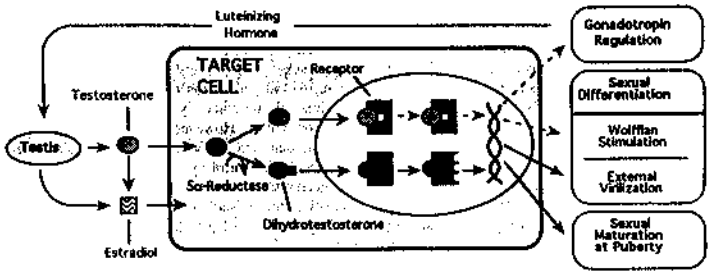
Fig. 12.23 Diagram showing the hormonal control of testicular function. Luteinizing hormone secreted by the anterior pituitary controls testosterone synthesis by the Leydig cells, which lie between seminiferous tubules; testosterone, in turn, exerts negative feedback on LH secretion. Testosterone controls the rate of spermatogenesis by acting upon Sertoli cells, but only appears to operate after the Sertoli cells have been primed by the action of FSH; secretion of this hormone appears to be controlled by negative feedback exerted by a protein known as 'inhibin', which is secreted by Sertoli cells in an amount related to the rate of spermatogenesis.

6) Prolactin and Gonadotropins

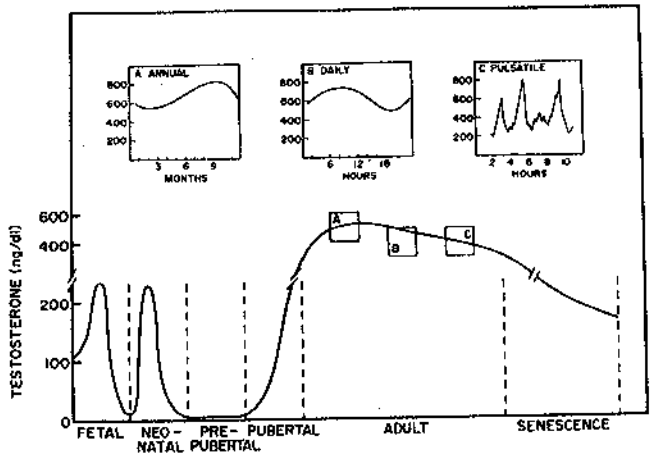
- hyperprolactinemia: associated with disturbed reproductive function reflected by a variety of symptoms and signs of hypogonadism
  low LH levels, low s-T levels
  --> H-P axis fails to respond to reduced testicular T production.
- Prolactin : inhibit GnRH secretion
  (directs or through modulation of the dopaminergic pathways)
  excessive prolactin may affect sexual functions by having a direct effect on the central nervous system and also by inhibition of androgen secretion.
- Bromocriptine : a dopamine agonist with prolactin-lowering activities
  improves sexual function

7) Androgen action

- Major function of androgen
  regulation of gonadotropin secretion
  initiation and maintenance of spermatogenesis
  formation of male phenotype during sexual differentiation
  promotion of sexual maturation at puberty and controlling sexual drive and potency



- Testosterone
  synthesized from pregnenolone within the Leydig cells
  생산: 5 -6 g/day
  secretion: irregular, pulsatile manner.
  diurnal pattern (peak level: early morning, nadir: evening)
  target cell: converted to DHT by 5-alpha reductase.
  T and DHT --> high-affinity-androgen receptor protein
  ---> biologic activity in androgen taget tissues
  (accessory organs of male reproduction)



testosterone 2%: free
30%-60%: SHBG
remainder: bound with much lower avidity to albumin and other proteins.
bioavailable T; free and albumin bound portions
--> modulate androgen function

- Estrogen
  secretion: directly by testes
  formed in peripheral tissues
  The mechanism by which estrogens act to augment or block androgen actions are still not fully understood.

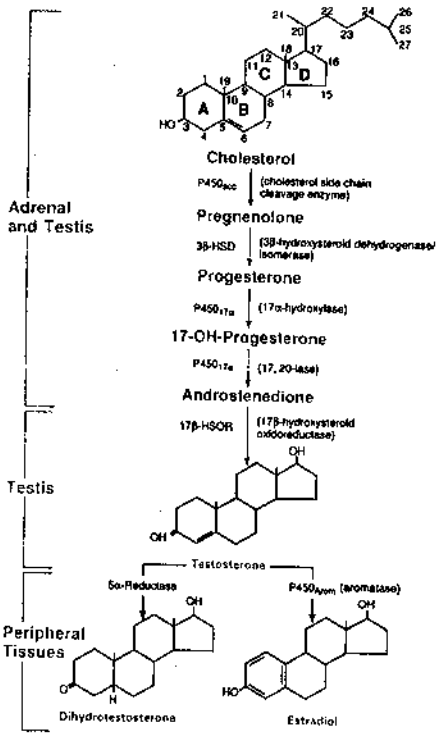


FIGURE 339-1 Pathways of androgen formation in the testis and the conversion of androgens to other active hormones in peripheral tissues.

8) Androgen target organs

- Androgen
  many important physiological actions
  --> effects on m. bone, CNS, prostate, bone marrow and sexual function.
  responsible for prenatal differentiation
  development of the male reproductive tract
  have a key role in both stimulating and maintaining sexual function in men
  increase nitrogen retention, lean body mass and body weight
  skeletal system: impact both on bone formation and bone resorption
  stimulatory effects on erythropoiesis
  have an effect on serum lipid --> lower plasma concentration of HDL
  higher concentration of TG, LDL and VLDL

9) Adrenal androgens

- higher brain centers
  --> hypothalamic corticotropin-releasing factor(CRF)
  --> ACTH
  --> adrenal gland (steroid synthesis and secretion)
- adrenal cortex
  DHEA, DHEAS and androstenedione secretion (not effective androgen).
  --> peripheral tissue: converted to potent androgens (T and DHT)
  significantly to circulating T levels in women, but not in men
- adrenal secretion (/day)

DHEA	3-4 mg
DHEAS	7-14 mg
androstenedion	1-1.5 mg
Testosterone	50 mcg

Relative Androgenic Activity of Adrenal Androgens

DHT	300
Testosterone	100
Androstenedione	10
DHEA, DHEAS	5

- DHEA, DHEAS, androstenedione : bound to albumin (90%) and SHBG (3%)
- DHEAS : most abundant steroid in circulation
  peak values: 20-30 대
  70대: 1/5 of peak value
- DHEA/DHEAS: multifunctional steroid
  protective roles in many aspects of cellular aging defects.
  many people are now taking DHEAS as a potential "fountain of youth"

6. PADAM. CLINICAL PICTURE

- In contrast to the menopause, the process of the andropause is characterized by an insidious onset and a very slow progression

Andropause syndrome

1) The easily recognized features of diminished sexual desire and erectile quality, particularly nocturnal erections
2) changes in mood with concomitant decreases in intellectual activity, spatial orientation ability, fatigue, depression and anger
3) decrease in lean body mass with associated diminution in muscle volume and strength
4) decrease in body hair and skin alterations
5) decreased bone mineral density resulting in osteoporosis
6) increase in visceral fat

7. BIOCHEMICAL ALTERATIONS

- significant inter-individual variability on the onset, speed and depth of the androgen decline associated with age and no factors have emerged that predict the characteristics or effects of the age-related hypotestosteronemia
- mean s-T level: decreases 1%/yr (지속적 현상 아님)
  biochemical hypogonadism 60세 이하: 7%
  60세 이상: 20%
  free & albumin-bound T: declined by approximately 1%/yr between 40-70 yrs
  (overall drop of nearly 1/3)
  SHBG: 나이가 들면서 증가 --> bio-available T 의 감소
  나이가 들면서 circadian rhythm의 소실 --> steady low levels of androgens

- extragonadal androgen production

DHEA: adrenal androgen, declined 3%/year, 3 times faster than free T, falling by age 70 to one-third of its serum concentration at age 40.

Its metabolite, DHEA sulfate, followed a similar course.

DHEA, DHEAS 의 감소 : parallel with a decrease in well being

Morlaes et al: supplimintal exogenous DHEA

--> improvementin quality of life parameters

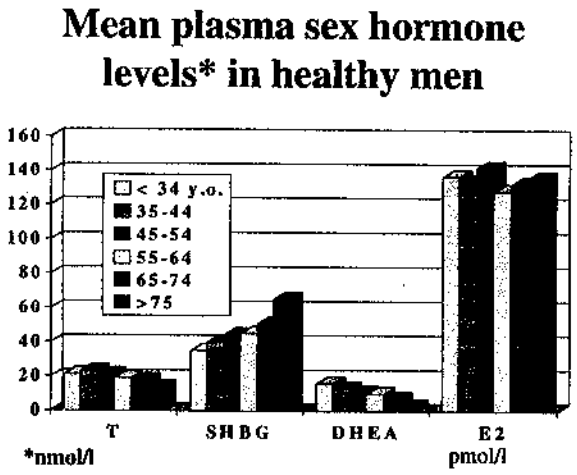


Figure 11. SHBG levels increase with age while E2 remains relatively stable

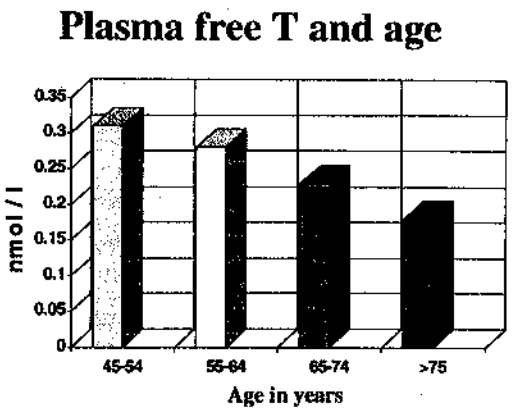


Figure 10. Decline of levels of free plasma T with age.

8. BIOCHEMICAL MANIFESTATIONS

- Establishing the presence of hypogonadism on purely clinical basis is, in most cases, extremely difficult. Only the most severe cases bring up clinical suspicion. Despite this, there is considerable controversy as to the need for hormonal evaluation on the senescent man.
- risk or suspected of hypogonadism.

biochemical evaluation

1) best initial laboratory test

: morning, nonfasting, plasma total T level

morning sample 이유)

circadian rhythm of T secretion in man

--> levels are highest in the early morning and can decrease by 35% in the midafternoon and evening.

60세 이상: may not be as important because the circadian rhythm in T secretion is blunted with age.

- Initial total T: subnormal --> should be repeated.
- clinically hypogonadism 의심

total T value: borderline (200-350 ng/dL, 7.0 -12.2 nM/L)

==> free or non-SHBG-bound T determination may be halpful.

cf) free T: portion of serum total T not bound to an protein (1-2% of total T)
non-SHBG-bound T : known as bioavailable T
portion of the total T that is not protein-bound (free)
plus that portion that is bound to albumin
albumin과 결합이 약하기에 사용가능
SHBG 과 결합한 T는 강하게 결합되어 있어서 사용 불가능

2) T levels : below or lower limit
--> LH, FSH and prolactin

3) plasma total T levels: less than 200 ng/dL(7.0 nM/L)
--> man is hypogonadal regardless of age
further evaluation for the cause of the hypogonadism (primary hypogonadism or testicular failure) is warranted.

4) older man: diagnostic lines are not as clearly defined and additional information may be needed.

8. TREATMENT

- Goals of treatment
: restoration of sexual functioning as well as libido and sense of well being
prevent or improve already established osteoporosis and optimize bone density
restore muscle strength and improve mental acuity

1) Oral androgen
① Fluoxymesterone, Methyltestosterone : hapatotoxicity, change in lipid profile
(LDL상승, HDL 감소 -> cardiovascular risk 증가)
② Testosterone undecanoate (Andriol) : 림프계를 통해 재흡수
free of liver toxicity
120-160mg/daily

2) Intramuscular injection
① Testosterone enanthate 200-250 mg / 2-3 weeks
② Testosterone cypionate 200 mg /2 weeks
--> 첫 3일내 최고치(1400 ng/ml)를 이루고, 정상범위의 상한치를 능가하게 되었다 가 2주 이내 hypogonadism 수준으로 감소.
생리적이지 않으므로 이상적이라 할 수 없다.
③ Testerone buciclate 1000 mg 1회 12주간 정상범위의 낮은 수준유지 (임상시험중)

3) Sublingual testosterone
Testosterone cyclodextrin
임상시험중, 3 time/day, T농도가 신속하게 상승하여 정상범위의 상한치에 이름.
장단점 평가 위해서는 더 많은 연구 필요

4) Transdermal testosterone

첫 번째 이용약제로 선택할 수 있다.

특히 T enanthate injection으로 증상의 기복이 있는 환자에게 적합.

① Transdermal patch (scrotal skin, Testoderm®)

10-15 mg T 함유, 매일 부착시 충분한 혈중 T 유지.

Nieschlag et al (Lancet, 1986)

10년 사용 경험 : 심각한 부작용 없이 충분한 장기적 대치효과

required weekly scrotal shaving (24시간 유지가 힘든 경우도 있음)

abnormal high DHT level (high concentration of 5-alpha reductase in the scrotal skin)

② Transdermal patch (non-scrotal skin, Androderm®)

2개의 patch를 매일 복부, 흉부, 어깨 뒷편에 부착.

혈중 농도를 생리적 수준으로 유지

Ozata et al (Endocrine J, 1997)

improvement in T levels associated with improved sexual function, libido, NPT response, with maintenance of normal hematocrit, lipid profile, PSA level, and prostate volume.

side effect: inconvenience of applying them

dermatitis (sometimes significant chemical burns)

5) Testosterone implants

6개월까지 생리적 수준의 T 치를 보장

--> 삽입을 위한 소수술과 감염, 제거의 문제

9. MONITORING PATIENTS ON TESTOSTERONE REPLACEMENT

1) 임상적 척도

- 보충요법의 효과를 알 수 있는 척도

improve psychologic well-being and mood.

increased muscle strength

성적 활동력, 성적사고, 공상 증가

2) 신체 척도

- 과체중 (복부지방 축적) : T 치가 낮은 남성에서 더 흔하게 나타남.

--> 보충시: 지방질 (특히 하복부) 감소시켜 여성형 체형이 남성화

Marin 등 (Obesity Res, 1993)

중년 복부비만 남자 대상

T undecanoate 80 mg 8 months 투여 후 CT 촬영

--> 대조군에 비해 내장 지방의 유의한 감소

- increase muscle mass and stemina

3) 검사실 척도

(1) serum Testosterone (free T, SHBG) level

이상적 보충요법: serum T 치가 생리 수준으로 유지.

(6-12 mons 간격으로 검사)

Total T 측정으로 충분 (예외: hyperthyroidism, 간질약 투약시, 심한 비만)

(2) Gonadotropins (LH, FSH)

primary or secondary hypogonadism 감별에 중요.

그러나 T monitoring 에서는 별로 중요하지 않다.

(3) Lipid profile and cardiovascular disease

- T 과 심혈관계 질환과는 아직 논란이 많다.

Hypogonadism 에서 T 보충서: cardiovascular dz. 증가시키지 않는다.

(TC, LDL: 감소, HDL: 변화 없음)

생리범위 이상 투여시: TC, LDL 증가, HDL 감소

--> 동맥경화증의 원인.

==> PADAM 환자에 대해서 esterified T를 보충하면 초기에는 정상범위보다 다량의 T를 보충함으로써 심혈관계에 좋지 않은 영향을 미칠 수 도 있다.

(4) Erythrocytosis

- 노령의 남성에서 T 보충요법: 혈청 hematocrit level 7%까지 상승시킴.

노령의 남성은 젊은 성인에 비해 약간 낮은 hematocrit 치를 갖고 있으므로 노인에서 T 의 적혈구 생성 촉진 작용은 일반적으로 유익할지 모르며, erythrocytosis가 문제를 일으키는 일의 없다.

--> 치료효과와 부작용을 알아보기 위해 3개월마다 이후 1년마다 hematocrit/ hemoglobin 검사

(5) Liver

- methylated form 사용시 나타남 (Fluoxymesterone, Methyltestosterone).

--> jaundice, alteration of liver function, hepatic carcinoma.

- injectable, dermal and oral agents (not employing methyl T): safe.
- 1년 간격으로 간 기능 검사를 시행하는 것이 좋다.

(6) Prostate

< BPH >

Douglas et al, J Surg Oncol, 1995

androgen administration: significant increase in prostate volume and PSA level

-> but within normal limits

most studies: no effect of exogenous androgens, PSA or prostate volume

< Prostate cancer >

- T promotes growth of an established adenocarcinoma is firmly established.

-Current knowledge

serum levels of sex hormones carry on relation to the development of prostate ca. and there is either no change or only a modest on (within normal range) increase in PSA after T administration.

- T치가 낮은 고령의 남자: occult prostate ca. 발생 --> 14%

고령 남성에서 T 보충전에 DRE, PSA, TRUS 등으로 prostate ca. 에 대한 evaluation 이 필요

T 보충후: rapid increase in PSA, detection of abnormalities in DRE
--> clear indication for further investigation

- 6개월 간격으로 추적검사

--> 추적검사중 : PSA 2.0 ng/ml 의 증가
0.75 ng/ml/year 이상 증가 (2년 이상)
==> 이때는 치료 중단.

(7) Bone density

- Oppenheim & Klibanski 1989

61세, 혈중 남성호르몬치 : 144 ng/dL 심한 성성기능저하증 환자
--> 같은 나이의 대조군 보다 골밀도가 낮은 환자 6명에게 남성호르몬 투여 6-8개월 후 모두에서 골밀도 증가.

- bone density: 노화에 의해 감소, 특히 hypogonadism 동반 노인에서 더 낮다.
--> T. 이 중요한 역할을 할지 모르나 이의 확진을 위해서는 많은 연구 필요.

(8) Sleep apnea

exacerbated during the administration of exogenous T
--> caution is indicated if androgens are prescribed for a patient with previously documented or suspected sleep apnea

10 RECOMENDATION

- Our understanding of PADAM is still incomplete and there exist a number of controversial issues in regard to hormonal replacement in elderly men.

therefore, standards and guidelines on the subject may be premature.

< Decalogue >

1. Men receiving exogenous T must have a clear indication for it
2. No patient is too old to receive T therapy if it is clearly indicated
3. men with suspected secondary hypogonadism (of H-P origin) should be thoroughly investigated before the onset of hormonal replacement
4. DRE and PSA determination are mandatory before starting androgen replacement therapy
5. men with mild LUTS may be suitable for androgen treatment while those with marked symptoms are not

6. known prostate or breast ca. are an absolute contraindication for T treatment
7. injectable or oral T esters as well as the dermal patches are recommended because of safety
8. 17-alkylated oral steroids are to be avoided due to their erratic absorption and potential for toxicity
9. For the first year after onset of therapy, patients should be followed quarterly to assess response to therapy (clinical and biochemical), DRE and PSA if older than 40 yrs of age. patients who remain stable may subsequently be followed annually, at which time other tests should include hemoglobin, liver function, lipid profile and serum calcium. Bone density, psychological evaluation , etc. should be done depending on the initial indications for androgen supplementation
10. serum levels of T will fluctuate considerable, particularly if the intramuscular administration in given. Regardless of T serum levels, clinical response is a better guide to dose requirements